GENETIC DETERMINANTS

Lung cancer is not an inevitable consequence of cigarette smoking. Thus, host factors, some which may be genetically determined, influence susceptibility of lung cancer. The same factors might also help determine whether an individual becomes a smoker. Familial occurrence of lung cancer is somewhat rare, though anecdotal reports appear regularly in the scientific literature (Li 1988). For example, Paul, et al (1987) recently reported about three brothers with alveolar cell carinoma which occurred when each reached approximately the same age.

Actually the first published epidemiologic evidence about genetic factors in the etiology of lung cancer appeared over twenty years ago (Tokuhata 1963, 1964). In this study, the mortality experience of blood relatives of 270 lung cancer patients was compared to that of an equal number of neighborhood controls matched by race, sex, age, and usual residence. Multiple contacts were used to help improve the reliability of smoking information not obtained directly from an index subject. Mortality from all causes combined and from all cancers

combined was greater among relatives of the lung cancer cases than among relatives of the controls. This excess was primarily in the brothers and mothers of the cases. Respiratory system cancers were significantly in excess among relatives of the lung cancer cases compared to controls; no other organ system demonstrated this difference. Threefold excess mortality from lung cancer was noted in the cases' relatives, and was more marked among males than females. This aggregation of familial lung cancer among relatives of lung cancer patients could not be accounted for by the effects of any of the variables not used for matching. It is unlikely to be due to similar occupational exposures, since the effect was also noted among females. Furthermore, air pollution or common environmental exposures are an unlikely explanation since controls were matched to cases by residence. These results might even be extended to non-malignant respiratory disease mortality, as an indicator of possible genetic predisposition to a variety of respiratory ailments, since case relatives demonstrated excess non-cancer respiratory diseases, as well. Because the blood relatives of cases tended to smoke, whereas the relatives of the controls did not, this study would also suggest that genetic factors have a role, not only in lung cancer etiology, but also

in a concomitant predisposition to smoking which would result in an overestimation of the lung cancer risk associated with smoking. The alternative explanation that, regardless of genetic predisposition, children of parents who smoke also would tend to smoke does not account for the fourfold excess among non-smoking relatives of cases.

Ooi, et al (1986), using relatives of spouses as a comparison group for relatives of lung cancer cases, also found excess risk of lung cancer among relatives of the cases. Cases were selected from death records in ten Louisiana parishes, and telephone or mail interviews were conducted to obtain information on tobacco usage, occupational exposures, and other factors. The study population thus comprised 336 cases (probands), 307 controls (spouses) and their families. Relatives of probands and controls did not differ appreciably with regard to smoking status, type of tobacco used, or duration of smoking. There were, however, significantly more proband relatives who smoked more than two packs-per-day and who smoked sixty or more pack/years. Regardless of their smoking status, relatives of probands had elevated lung cancer relative risks compared to

relatives of spouses. These risks were statistically significantly elevated for both sexes among smoking relatives, and for females among non-smoking relatives. The greatest risk (RR=4.6) was found among the probands' female relatives who never smoked, in agreement with the magnitude of the effect found in Tokuhata's study. Logistic regression analysis was used to control for the effect of other factors, and the familial factor remained a significant determinant of risk even when smoking and these other factors were eliminated. The study had no obvious major methodological faults, and the likelihood of response bias was minimized by reliability checks, although lung cancer cases' surviving spouses and relatives might intentionally or unintentionally distort the probands' or their own smoking history in some non-random manner. It is also possible that differential responses might have occurred due to the probands' information always being obtained from surrogate respondents, while spouses' information was, usually obtained directly. Furthermore, a larger proportion of the spouses' relatives were alive than were probands', and this might have resulted in differential accuracy of the information obtained. The authors suggest that their findings "may be interpreted to support the

presence of a susceptibility gene to lung cancer." However, the finding of increased prevalence of other cancers among probands' families appears to indicate increased susceptibility to several types of cancers. A report from the same study on the risk of non-lung cancer among relatives of lung cancer patients demonstrates greater risk for these cancers among more members of the proband's families (Sellers 1987). Nevertheless, the bulk of the excess cancers among probands' relatives was for sites usually associated with smoking, i.e. lung, nasal cavity, larynx, and cervix.

The mechanisms for development of some neoplastic disease are thought at the molecular level to be related to the activation of certain genes (proto-oncogenes) into "oncogenes" with structural abnormalities that make them contribute to the process of malignant transformation (Rodenhuis 1987). The oncogenes that appear to have a role in human lung cancer are members of the families of genes called myc and ras. Rodenhuis, et al (1987) studied the prevalence of mutational activity of ras oncogenes in tumor specimens of untreated non-small-cell lung cancer. They detected mutational activity of the K-ras gene in five of 35 specimens; all 5 were adenocarcinomas. The

five patients from which these specimens were taken were heavy smokers, whereas two of the patients with a K-ras-negative adenocarcinoma had never smoked. Although this series is small, it does point out differences at the molecular level, reflected in differential ability for K-ras mutational activity, that also are related to cigarette smoking status.

Samet, et al (1986) compared familial and personal respiratory disease histories of lung cancer cases ascertained by a state-wide tumor registry, and matched control subjects selected randomly from lists of telephone numbers and Medicare participants. Subjects or their surrogates were interviewed about tobacco use, residential and occupational history, diet, occupation, and disease history. An analysis of the 518 cases and the 769 controls demonstrated significantly higher prevalence of lung cancer and "other unspecified cancers" in parents of the cases compared with parents of the controls. No difference in prevalence was noted for cancers in grandparents of the two groups. Multiple logistic regression analysis revealed a significantly elevated odds ratio (5.31, CI=2.21-12.76) for parental history of lung cancer. This type of analysis

adjusted for cigarette smoking by the subjects, and thus should not reflect concordance of smoking habits between parents and children. The study used self-reports for control subjects and both self and surrogate-reported information which could not be checked for reliability. Given that the study contrasted diseased cases with healthy controls, it is possible that information bias due either to the different types of respondents or to their different health status might partially account for the observed results.

A recent brief report from a similar epidemiologic study confirms these findings. Kramer, et al (1987) compared lung cancer incidence over a twenty-five year period among first-degree relatives of lung cancer patients and among controls. A significantly increased twofold risk was found for relatives of the cases. The relative risk was higher among non-smoking relatives, and highest among non-smoking relatives of smoking cases. The authors suggest that these results indicate a lung cancer aggregation in families which is only partially due to a familial tendency to smoke.

Among the host factors studied for their influence on susceptibility to lung cancer are the genes controlling the enzymatic oxidative metabolism of chemicals (procarcinogens) by enhancement of metabolic activation, or by inactivation of activated metabolites. Clearly, the actions of these enzyme systems relate to genetic predisposition to cell types associated with smoking (i.e. squamous cell and small cell carcinomas), although Yoneyama, et al (1986) have demonstrated a potential genetic basis for adenocarcinoma of the lung among non-smokers. One enzyme system, the aryl hydrocarbon hydroxylases (AHH), has been studied extensively, in part because its induction is controlled by a single gene locus in mice. However, in man several AHH enzymes exist, each controlled by a different gene, and results relating AHH activity or AHH inducibility to lung cancer in humans have been inconsistent (McLemore 1981, Rudiger 1985). Rather than the activity of individual enzymes, Rudiger, Nowak and others compared the amount of relevant activated metabolites, determined as DNA adducts, in monocytes of lung cancer patients and healthy controls (Rudiger, et al 1985, Nowak 1987). They found, in concordance with results from in-vivo and epidemiologic studies on metabolic oxidation of debrisoquine (a

non-toxic test compound) (Ayesh 1984, Idle 1983), that patients considered to be cancer-prone showed approximately twice as much of activated metabolites as the controls. As expected, no differences were found between smokers and non-smokers. It seems possible that the increased adduct concentrations were due to the disease, rather than being a cause of the disease. The authors, citing only a slight elevation in adduct levels in patients with a family history of cancer, argue, somewhat unconvincingly, against this. Seidegard, et al (1986) studied the occurrence of the comparative distributions of the activity of glutathione transferase (towards trans-stilbene oxide as substrate, GTtSBO), a Phase II enzyme controlling the detoxication of reactive intermediates of oxidative metabolism, among lung cancer patients and controls. They found a greater proportion (59.0%) of the controls who smoked had GTtSBO than did lung cancer patients who smoked (34.8%). This difference was statistically significant among heavy smokers. Thus, these data suggest a biological mechanism for increased susceptibility of some individuals to smoking-induced lung cancer, since many potentially carcinogenic components of cigarette smoke are known to be conjugated by glutathione transferase.

Substantial evidence exists to support the conclusion that lung cancer is largely a genetic disease (Hansen 1987). Although the magnitude of the genetic component of lung cancer etiology probably is in the order of a 10-100 times higher incidence among susceptibles, this effect "can be surprisingly difficult to detect"....but "may account for a substantial proportion" of lung cancers (Peto 1980). Recently, it has been reported that a genetic defect in chromosome 3 contributes to the development of small cell lung cancer, a type of the disease which accounts for 30,000 to 40,000 cases annually. The involvement of chromosome 7 in non-small cell lung cancer has been suggested by Lee, et al (1987). Other data suggest that there are financial factors in serum selenium and Vitamin E levels of lung cancer patients (Miyamoto 1987) which may reflect on interaction between a genetic and a dietary etiological components.

DIETARY INFLUENCES

Several retrospective and prospective epidemiologic studies have consistently shown a relationship between certain dietary components and reduced risk of lung cancer (Colditz 1987, Byers 1987, Wu 1988, Koo 1988). Within the last few years, additional studies have confirmed these observations, refined the association with specific components of the diet, and demonstrated how smoking-related risk might be misinterpreted because population studies have not accounted for dietary differences.

The importance of dietary factors, including cooking practices, in the etiology of lung cancer is underscored by recent results from a case-control study among women in China (where few women smoke cigarettes) (Gao 1987). This study found an association between lung cancer and exposure to cooking oil vapors, prompting the authors to suggest that factors other than smoking are responsible for the high lung cancer risk in Chinese women.

In the NHANES I Epidemiologic Follow-up Study, a cohort study based on the National Health and Nutrition Examination Survey conducted from 1971-1975 on a probability sample of the non-institutionalized U.S. population, Shatzkin, et al (1987a) calculated cancer incidence and mortality rates among persons with different serum cholesterol levels. Data on age, education, smoking, alcohol consumption, etc. were collected by personal interview, and cholesterol level was determined from collected blood samples. Median follow-up time from the initial interview was 10 years for the 5,125 males and 7,363 females in the incidence analyses and for the 5,791 males and 8,535 females in the mortality portion. The results demonstrated an inverse association between cholesterol level (by quintile) and leukemia, lung cancer, bladder cancer, and pancreatic cancer in both sexes, and cervical cancer in women. Cancer risk among men in the lowest quintile was almost double that of men in the highest quintile for both incidence and mortality. Among women, the mortality risk was the same as among males, but the incidence in the lowest quintile was only 1.2 times higher than the highest quintile. These results are unlikely to reflect a "preclinical cancer effect", i.e. decreased total serum cholesterol as a result of

cancer, since the inverse relationship was strongest for cancers diagnosed 6 years or more after cholesterol was measured, and did not diminish with increasing time between determination of cholesterol and diagnosis of cancer. Because the inverse relationship was especially prominent for the so-called "smoking-related" cancers, with a relative risk of 2.0 (1.3-3.0) for the lowest compared to highest quintile (Shatzkin 1987b), the likelihood of a biased association with smoking is evident.

This inverse association must be considered along with data from Wynder, et al (1987) which show a highly statistically significant international correlation between the proportion of calories from dietary fat and lung cancer mortality. This analysis accounted for smoking by including tobacco disappearance data from each of the 43 countries in the study. Several potential biological mechanisms exist for the initiation or promotion of lung cancer by a high-fat diet, and the literature is replete with experimental evidence of its carcinogenicity. The apparent anomaly with the findings of Shatzkin, et al (1987) probably reflects the importance of genetic and other factors in addition to cholesterol intake in determining serum

cholesterol level. In any event, these two studies demonstrate the potential effects of cholesterol level and fat intake on lung cancer risk, although other dietary factors are important, as well.

In a carefully conducted recent study (Byers 1987), a modified food frequency method was used to obtain information on usual diet (prior to one year before onset of symptoms) from 450 incident lung cancer cases, and from 902 general population control subjects. The need for gathering information on other potential risk factors resulted in a rather long interview which could only be administered to patients tolerant subjects. Consistent with previous studies of the same design, this investigation found an inverse relationship between intake of vitamin A from fruits and vegetables (carotene) and lung cancer risk. The association was strongest (i.e. the risk was reduced most; about 50-80%) for squamous cell carcinoma, in concordance with previous results (Kvale 1983, Byers 1984, Zeigler 1984), and also for older males, male ex-smokers, and for male current smokers with less cumulative lifetime cigarette exposure. Neither vitamin E nor vitamin A from animal sources (retinol) resulted in a risk reduction. It is possible, because of the selection criteria for this

study, that bias was introduced by excluding the most ill cases or those who died before they could be interviewed. Dietary recall may have been different between cases and controls due to knowledge of their disease status or to the slightly different time periods involved. Furthermore, less than half of the eligible controls completed their interview, and if their non-participation were related to dietary practices, this could represent an additional source of bias.

Zeigler, et al (1986), in the largest study of diet and lung cancer to-date found very similar results. Their population-based case-control study among men in New Jersey included 763 cases and 900 controls who has been interviewed approximately four years earlier about their usual frequency of consumption of 44 food items. In concordance with Byers, et al (1984), they found no association between lung cancer and intake of retinol or total vitamin A, but did find a 30% (non-significant) excess risk associated with low or medium intake of carotene. A statistically significant trend in reduced risk associated with increasing carotene intake was found among current smokers and ex-smokers of one year or less. They also found that the reduced risk was most apparent for squamous

cell carcinomas, although it extended to other cell types when only current and recent smokers were analyzed. In addition, the study found that intake of dark green leafy vegetables offered a greater protective effect than did intake of retinol. The highest consumption of vegetables was found among non-smokers, and tended to decrease with increasing duration of smoking. Intensity of smoking was not related to consumption of vegetables. While the influence of vegetable intake on the risk of lung cancer is not very strong, (RR=1.38 for lowest vs highest consumption after adjusting for smoking), the large percentage of the population with low consumption results in a lung cancer population-attributable risk of 22%. One possible source of bias in this study is the use of licensed drivers as controls. These people probably represent a different population from the case source, and may have introduced some non-comparability in dietary habits, recall, or unmeasured potentially confounding factors.

Pastorino, et al (1987) compared the serum levels and dietary intakes of retinol and carotene of 47 females with histologically confirmed lung cancer with those of 159 hospital controls. Blood samples taken the day after admission and dietary history questionnaires

administered by dieticians were used for the determination of vitamin A intake and serum level. Odds ratios calculated by comparing tertiles of retinol and beta-carotene in serum and diet (controlling for cholesterol, triglycerides, etc.) were elevated for the lowest vs the highest blood and intake levels. The ORs for plasma carotene were statistically significant for the combined low and medium tertiles compared to the highest, as was the trend. Though not significant, there was a trend of increasing risk with decreasing serum and dietary retinol and with dietary carotene. Interestingly, the authors noted that in this study, women who smoked for less than 25 years or who smoked less than 20 cigarettes per day, had half the lung cancer risk of non-smokers.

The protective effect of vitamin A on lung cancer risk also was observed in a population quite different from those discussed above. Kolonel, et al (1985) conducted a lung cancer case-control study in Hawaii, using tumor registry-identified cases and age- and sex-matched controls selected by random digit dialing. Spouses served as surrogate respondents for 24% of the cases. Based on interview data collected on 364 patients and 627 controls, an odds ratio in males of

1.8 (1.1-3.1) was calculated for the lowest vs the highest intake group, with a clear dose-response effect based on weekly total vitamin A intake. No effect of vitamin A was found in females. Analyses based on vitamin A food sources only, or on retinol sources only yielded similar results. Though no data were presented, the authors noted that results among cigarette smokers were similar to those found in the male subjects.

In a study examining the role of vitamin A as a risk factor for cancer of any site, Middleton, et al (1986) confirmed previous observations made on lung cancer patients only. The relative risk was 34% lower among males with the highest intake level vs the those with lowest level. After adjustment for smoking the risk was 27% lower. A statistically significant dose-response relationship also was noted. In females, a slight, non-significant risk reduction was seen. Interestingly, in males vitamin A showed a protective effect specifically for several sites which have been associated with smoking. This may account for the apparent sex-specific effect on these squamous cell tumors, given the different smoking habits of males and females. With so many sites included in this study, it is

possible that some statistically significant associations actually were due to chance. In addition, because information was collected on dietary habits one year prior to symptoms onset, the relevance of these data for etiological aspects is questionable since lung cancer generally has a rather longer latency period.

The apparent inverse association between vitamin A intake or serum level and lung cancer risk is particularly important in the context of our extended appraisal because it demonstrates a reasonable pathway which leads to the spurious indictment of smoking. Cross-sectional studies have shown lower plasma levels of beta-carotene in smokers compared to non-smokers (Stryker 1988, Aoki 1987). In turn, this has led to suggestions that one way in which smoking might affect lung cancer risk is by reducing the level of protection associated with higher intakes of vitamin A. However, closer examination of the aforementioned reports reveals that alcohol consumption has a much larger effect on lowering serum vitamin A levels than does smoking. Thus, the apparent association of smoking with lowered vitamin A levels probably reflects, to a great degree, the strong correlation between alcohol and tobacco usage. Furthermore,

it may reflect a particular lifestyle which includes lower intake of leafy green vegetables and other sources of dietary vitamin A, which in turn comprises certain activities, propensities, or genetic predispositions which might be independently associated with increased risk of lung cancer. A recent comparison of the dietary habits of smokers and non-smokers in Great Britain exemplifies these differences (Whichelow 1988). In this study, approximately 9,000 randomly-chosen adults were interviewed about their dietary, smoking, alcohol and exercise habits. The investigators found definitive differences between smokers and non-smokers in eating behaviors which manifested themselves in a pattern of a typically unhealthy diet. Of particular pertinence are the findings that the diets of ex-smokers was similar to that of never-smokers, and that the diets of heavy smokers differed more from that of non-smokers than did the diets of light-smokers.

Based on estimates advertised by the U.S. Environmental Protection Agency (EPA), a substantial portion of lung cancer incidence in this country is due to exposure to radon in the domestic environment. These estimates are rather controversial, and exemplify the non-scientific factors which affect government-promulgated estimates of the risks to health from a variety of sources. For example, a recent Science article trumpets in its headline, "The radon seeping into homes may be killing 5,000 to 20,000 Americans per year; the best action may be to stop smoking" (Kerr 1988). As incongruous as this sounds, it becomes ludicrous when one reads the articles and notes that this mitigating strategy derives from a National Research Council committee which "assumed that radon risk multiplies the existing risk of dying of lung cancer...". The article continues, noting "In fact, the data did not best fit such a purely multiplicative model." The EPA has estimated that 5,000 to 20,000 lung cancer deaths each year are caused by radon (US EPA 1987). Following a 10-state survey of radon levels, the EPA revised its estimates of the number of homes with potentially dangerous levels upward by about

a factor of two. Yet, the estimated number of attributable cancer deaths remained the same (perhaps because upward revision would have accounted for 31% of all lung cancer deaths). Apart from the internal economies of the EPA which drive their estimation procedures, the problems with estimation of lung cancer population-attributable-risk due to exposure to radon in the home also derive from several scientific considerations: 1) The estimates are based on extrapolation from epidemiologic studies of uranium miners; 2) No representative sampling of radon levels in U.S. homes which takes account of seasonal, diurnal, and intra- and inter-house variation has been completed; 3) The distribution of homes with high radon levels is not uniform across the U.S., and attribution of 20% of lung cancers to exposure to radon thus implies a substantially higher proportion in some areas of the country; and 4) Only recently has any study of lung cancer due to residential radon exposure, which would allow the extrapolations to be verified, been published. It is worthwhile to expand on these considerations to appreciate fully the nature of the radon/lung cancer association.

Firstly, radon daughter dosimetry is very difficult because it involves a combination of factors such as respiration rates, particle size distribution, lung deposition, and Rn/Rn daughter equilibrium (Hornung 1987). Secondly, the miners' exposures were derived not only from actual measurements, but more often by extrapolation over time, estimation by geographic area, and estimates of early (before 1950) exposure based on knowledge of ore bodies, ventilation practices, and earlier measurements (Lundin 1971, Sevc 1988). Actual measurements were available only about 10% of the time, and the overall error in exposure measurement has been estimated at 137% (coefficient of variation) or about a 97% relative standard deviation of the total (working level month) for each miner (Hornung 1987). The extrapolation of risk derived from the miner studies to estimate risks due to exposure in the home introduces additional problems. In contrast to the population most highly exposed in the home, miners comprised males performing heavy manual labor in a very dusty environment. Risk estimates derived from this population, therefore, could be expected to overestimate the risk due to domestic exposure, even if the radon levels in the home were the same as in the mines.

Although a systematic appraisal of radon levels in U.S. homes has never been conducted, some estimates of these concentrations do exist. Nero, et al (1986) estimated the distribution of radon levels in U.S. homes from data on 38 areas, none of which were selected using statistically-based sampling procedures. These measurements typically were made in homes of volunteers, with expectedly higher levels, and by a variety of methods with differential validity and reliability. Arithmetic mean Rn222 levels ranged from 2.57 picocuries per liter (1377 homes) to 1.42 for those sites not having a prior expectation of high concentrations (817 homes). According to Nero, et al, these levels translate into a lifetime lung cancer risk of 0.3% (the EPA estimates it as 1.0%), or about 10,000 cases of lung cancer annually.

The study by Svensson, et al (1987) represents the first epidemiologic evidence of a relationship between exposure to radon at levels commonly encountered in the home and bronchial cancer. 292 female lung cancer cases identified from a local cancer registry, and 584 population controls constituted the study population. The cases

were restricted to women with cancers of the "unspecified epithelial group." Homes in which cases or controls had lived for at least two years were dichotomized by geological criteria and by whether the subject had lived close to the ground floor, into categories of "radon risk" or "no radon risk." All radon-positive homes and some of the negative homes (about 10% of the total number of addresses) were measured for radon level by a grab-sample technique. Data on the subjects' smoking habits were not obtained, although information from a national survey in 1963 was used as an estimate. Statistical analyses revealed a relative risk of 2.2 (1.2-4.0) for exposure to radon, or 4.1% of the cases attributable to that exposure. However, when actual measurements were used, the differences in radon/radon daughter concentrations between residences of cases and residences of controls were not statistically significant. The available smoking data indicated that smoking among women was not more common in the areas where higher radon levels were estimated, so the possibility of confounding is lessened somewhat. However, it is known that the presence of a smoker in a residence can affect radon levels, and this information is lacking in this study. It is not even clear just how smoking affects radon dose; some believe passive smoking increases

lung dose by increasing the equilibrium ratio of radon daughters (Winters 1983), while other evidence points to lower levels of total body contamination in smokers (Stebbings 1986). Evidence from experimental studies in dogs shows that cigarette smoke plays a protective role in suppressing radon-daughter-induced lung consequences (Gies 1988). In fact, depending on how smoking is factored into a radon risk assessment, the process introduces a range of risks over an order of magnitude (Ginevan 1986).

Since it is the polonium decay products of radon (Po-218 and Po-214), that deposit on the bronchial airways and deliver the carcinogenic dose (Harley 1986), it has even been suggested (Ravenholt 1987) that tobacco smoke containing polonium (Po-210) is a major source of the alpha particle activity attributed to radon. However, Letourneau, et al (1987) have shown that, in fact, the alpha particle activity inside a house is by four orders of magnitude predominantly due to radon and its short-lived progeny.

In the Svensson, et al study, the absence of actual radon daughter measurements on all residences is a most serious shortcoming, and

the grab-sample technique used for the study, is unreliable because levels vary from house-to-house and over short periods of time. It is generally accepted that the magnitude of radon levels in homes, which depends on house-to-soil coupling, soil moisture, indoor-outdoor pressure differences, air-exchange rate, etc. cannot be predicted very well either by geological criteria or proximity to homes with known radon levels.

Nevertheless, Stockwell, et at (1988) conducted a case-control study to determine if residence in an area with high natural radioactivity (i.e. with a large percentage of homes built on land reclaimed after mining of phosphate deposits containing uranium and members of its decay series) is associated with increased lung cancer risk. Actual levels of radon in homes were not measured. Male nonsmoking residents of the area were at elevated risk for all lung cancer, and specifically for adenocarcinoma, squamous cell carcinoma, and small cell carcinoma compared to residents of other parts of Florida. No statistically significant excess risks were found for male smokers or for females. The study suffers from not having actual measurements or radon levels lung cancer cell types was attempted.

OCCUPATION

Increased risk of lung cancer is associated with employment in a variety of industries. Among the jobs known to be at elevated risk are pesticide production, coke oven operation, roofing, mining, chemical industry, smelting, beryllium production, metal industry, shipyards, and dry cleaning. Recently, Simonato, et al (1988) attempted a systematic evaluation of the proportion of lung cancers due to occupational exposure by calculating population attributable risks from data in published studies. The authors' estimates were in the same general as commonly accepted, centering around 15%. They concluded that for selected populations residing in specific areas, the proportion of lung cancers attributable to occupation could be as high as 40%. A few recent studies suffice to exemplify the risk due to occupation, and the wide range of jobs associated with increased risk. Ronco, et al (1988) examined lung cancer and occupation in two industrialized areas of Northern Italy. Attributable risk percentages for occupation in the two areas were about 36% and 12%. Among the job categories showing excess risk were structural mental work, welding, electrical machine production, woodworking, and cleaning services. Carstensen, et al (1988) found excess lung cancer risk

among a cohort of Swedish bakers and pastry cooks. Wicklung, et al (1988) found an excess among orchardists in Washington State. They had hypothesized that any excess would be due to lead arsenate exposure, but a comparison of lung cancer cases and controls found no difference in presence, intensity, or duration of such exposure. The excess risk could not be attributed to cigarette smoking, and its cause remains unknown. A retrospective cohort study of marine engineers and machinists in Iceland found statistically significantly elevated lung cancer mortality risk to these occupations (Rafnsson 1988). Enterline, et al (1988) updated an earlier study of mineral fiber workers, and confirmed their excess respiratory cancer risk. The excess risk appeared to be specific for mineral wool workers but not for fibrous glass workers. Exposure to mineral oils from employment in a Norwegian plant which manufactured high voltage wires was found by Ronneberg, et al (1988) to increase the risk of lung cancer. Oil impregnated paper insulation for the cables was the source of the exposure. Pipefitters and platers in Finnish shipyards had excess risk of lung cancer incidence compared to regional urban rates (Tola 1988). In France, excess risk of lung cancer was found to be associated with employment as farmers, miners and quarrymen,

plumbers and pipefitters, and motor vehicle drivers (Benhamou 1988).

The variety of occupations in which the risk of lung cancer is elevated is clear. In addition to limiting the possible contribution of smoking to lung cancer causation, the occupational factor provides a pathway for smoking to be wrongfully implicated as a cause. This could occur if persons employed in occupations with higher risk of lung cancer happen to smoke more than persons employed in lower-risk jobs. Confounding of sort would not be unexpected since both occupation and smoking behavior are related to social class, as shown in a recent (Brackbill 1988) analysis of data from the National Health Interview Survey. Stellman, et al (1988) investigated this phenomenon in a population enrolled in the American Cancer Society's large prospective survey. They found that smoking rates were significantly higher in groups exposed to a variety of occupational hazards than in non-exposed groups. The differences were most notable for men, particularly for those exposed to asbestos, coal or stone dust, dyes, textile fibers, and chemicals or coal tar pitch.

CONCLUSIONS

The number of cancer deaths in the United States attributable to smoking is not as clear-cut as generally assumed. Based on rates from the National Cancer Institute's SEER program, the American Cancer Society estimates that 130,100 lung cancer deaths occurred in 1986 (American Cancer Society 1986). The estimated number of cases in 1986 was 149,000. The EPA estimates for the number of lung cancer deaths due to radon exposure are undoubtedly high at 20,000 (15.4%), and may be more realistic at 4% or 5,200. If, as suggested in the literature, occupational exposures account for another 15% (19,500), and diet for 20% (26,000), it is unlikely that smoking could be responsible for even half of the U.S. lung cancer deaths. This does not consider the effects of urbanization, stress, and air pollution. Furthermore, it neglects the evidence for a detection bias in the diagnosis of lung cancer, in which non-smokers are less likely to have _____ cytology performed (Wells 1988) and lung cancer is 37 times more likely to be correctly diagnosed in smokers than in non-smokers (McFarlane 1986a,b). Of course, this bias would result in falsely high estimates of the actual magnitude of the

smoking/lung cancer association. It does not take into account the familial host-susceptibility factor evident from genetic epidemiologic studies which "must have a substantial influence on lung cancer mortality" (Lynch 1981). Nor does it account for the effect of mineral particle deposition (Chung 1988). Finally, it fails to consider the potential effects of climatic and ecologic conditions, as demonstrated by Weinberg, et al (1987).

Therefore, "risk factor" most lay people assume to predominantly "cause" lung cancer may not even be the major "cause" of the disease. Support for this argument derives from descriptive epidemiologic evidence about the distribution of the disease and it's component cell types in time and among different population groups, and from a substantial amount of scientific literature detailing other major risk factors. Clearly genetic predisposition to lung cancer and to neoplastic diseases of other sites contributes greatly to the etiology of these diseases. Dietary habits and occupational exposures are well-documented as risk factors, and radon exposure has lately been taking on increased significance. Since these risk factors are comparatively difficult to measure, and usually have not been

adequately, if at all, taken into account in the case-control studies of smoking which have formed the basis for smoking risk estimates, these estimates must be erroneous. Certainly, there are other factors such as detection bias which contribute to lung cancer incidence and to a spurious implication of smoking. While information about risk factors other than smoking permeates the scientific literature, the public seemingly is unaware of its existence. This literature is recent, funded from a variety of sources, and has been reviewed herein with if anything, a bias toward conservatism, (witness the downgrading of the EPA estimates of the number of lung cancer cases attributable to radon). Thus in the end, when one considers the global picture, the commonly attributed role of cigarette smoking as a possible risk factor for lung cancer must be an overestimate.

Although there exists some perception of an etiological role for smoking in asthma, scientific evidence strongly disputes this. A national survey of asthma prevalence in the U.S. found asthmatics to be current smokers as frequently as non-asthmatics (Gergen 1988). In the published report of this survey, the authors noted similar observations reported from Australia and England.

In addition, two New Zealand studies, one on national asthma mortality and the other a regional case-control investigation, found young age, non-Caucasian race, and poor medical care to be associated with an increased risk of death among persons with asthma. (Sears 1987; Morse 1987a,b) Neither age at onset of asthma, family history of asthma, nor smoking habits were associated with increased mortality risk. In Papua New Guinea, a 15-year prospective follow-up study of mortality from chronic lung disease found no association whatever between smoking and severe respiratory symptoms or reduced lung function (Anderson 1988).

Non-specific bronchial hyper-responsiveness (BHR) is regarded as critical to the development of symptoms in asthmatics. It may also occur transiently after a respiratory infection or exposure to ozone, or

chronically due to immunologic sensitivity to substances such as western red cedar (Vedal 1988). The tree main theories for the origin of BHR are allergy, inflammation, and altered geometry. Pride (1987, 1988) found slight abnormalities in eosinophil count and IgE levels in smokers, but could not relate these to the presence of BHR. He found nothing to confirm an association between chronic inflammation of bronchial walls in smokers and BHR. Suzuki, et al (1988) found that the smoking of a single cigarette by healthy non-smokers did not change their bronchial responsiveness.

Since 1963, it has been known that decreased protease inhibition is associated with the pathogenesis of emphysema. This protease inhibition is due to a homozygous genetic deficiency of alpha-1-antiprotease (AAP) which allows enzymatic action on lung elastin. (Idell 1987) Recently, Satoh, et al (1988) have identified a single base substitution causing AAP deficiency in addition to previously identified homozygotic mutations causing identical respiratory consequences. The symptoms of emphysema associated with AAP deficiency begin before the age of 40 in most cases, and before the age of 50 in almost all. However, while individuals with certain inherited combinations of the alpha-1-antiprotease gene invariably develop emphysema, not all AAP-deficient individuals eventually develop the disease. In contrast to the obvious explanation in genetics, it has

been suggested that an effect of cigarette smoking is to increase the load of protease which must be inactivated and decrease the level of AAP. However, this hypothesis does not explain why emphysema does not develop in all cigarette smokers. According to Resendes (1987), "Although many explanations have been offered, this question remains unanswered."

There is evidence in the scientific literature that smoking-induced processes protect the lung against certain environmental hazards. This hypothesis was suggested some 30 years ago as an explanation of the observation that coal miners with bronchitis appeared to develop less pneumoconiosis than miners without the bronchitis. Sterling (1983) has hypothesized that one result of smoking is production of a layer of mucus which, by lining the respiratory tract, blocks the access of a potential carcinogen to the mucus membrane, or dilutes and clears these substances more effectively than normal. Albert, et al (1975) studied short-term bronchial clearance in nine non-smokers and six smokers. By comparing the clearance times of two radioactively-tagged aerosols, the second followed soon by the smoking of two to seven cigarettes, they found that in both smokers and non-smokers cigarette smoking resulted in a least a twofold speed-up in deep bronchial clearance. They postulated that an

increased mucus production was related to the observed effect on particle clearance.

Other investigators have found a qualitative difference in the composition of bronchial mucus between smokers and non-smokers. (Kollerstrom 1977) The acid mucins synthesized by the cells of the bronchial glands have either sialic (neuraminic acid) groups or sulphate groups on their side chains. The ratio of the amount of sulphated to sialic acid mucin was greater in smokers that in non-smokers, and clearly distinguished the two groups. The practical significance of this difference, however, is not clear.

Whether the mechanism is, in fact, related to increased clearance ability or to some immunologic response, smoking also appears to offer protection from other respiratory diseases. Extrinsic allergic alveolitis is one cause of pulmonary alveolar fibrosis, and is a result of an excess immune response to inhaled antigens. Warren, et al (1975), noted in their studies of lung mechanics of patients with extrinsic allergic alveolitis that most were non-smokers. Subsequently, Warren (1977) compared smoking histories of patients diagnosed with this disease with histories of patients with cryptogenic alveolitis or sarcoidosis and also with information obtained from a random sample of the local Manitoba population and

a group of 100 farmers entering the hospital with any diagnosis. Smoking habits among men with extrinsic allergic alveolitis differed significantly from those of the other two disease categories combined. The proportion of non-smokers in the allergic alveolitis group was significantly greater than in the local population or the group of farmers. All females with allergic alveolitis were non-smokers.

ESTROGEN DEPENDENT CANCERS

SMOKING AND ESTROGEN SECRETION

Smoking has been shown to have an hormonally mediated effect on reducing the risk of cancers of the breast and endometrium. MacMahon, et al (1982) demonstrated a reduced excretion of endogenous estrogens in urine samples from women who smoked; Greenberg, et al (1987) found that hormonal replacement therapy users were more likely to smoke than were non-users; Jick, et al (1977) showed that smokers experienced menopause at an earlier age. Interestingly, Hartz, et al (1987) recently found that smoking was associated not only with early natural menopause (age-adjusted OR=1.6) but also with surgically induced menopause (OR=1.5).

Prior to menopause, the ovaries are the source of estrone and estradiol, while after menopause, the principal source of endogenous estrogens is through conversion of androstenedione, produced by the adrenals. Fat mass, a known endometrial cancer risk factor, is a major determinant of this conversion to estrone. Jensen, et al (1985)

examined 136 post-menopausal women treated with exogenous estrogens to determine the effect of smoking on serum levels of estrone and estradiol. They found reduced levels of both hormones in smokers, particularly among women taking higher doses of exogenous estrogens. There was a statistically significant inverse dose-response relationship between amount smoked and serum estrogen level, with smoking having no effect among women not taking exogenous estrogens. The authors suggest that the lower estrogen levels in smokers result from increased metabolism of estrogens in the liver, rather than lower estrogen production as suggested by MacMahon, et al (1982) in their study of pre-menopausal women.

Michnovicz, et al (1986) demonstrated that smoking leads to decreased bioavailability of the estradiol metabolites which possess potent estrogenicity. Daniell (1987) contends that if this were the case, administration of exogenous estrogens would override this deficit. Thus, estrogen antagonists, which may either be absorbed during tobacco usage or produced in the body during smoking, substantially contribute to the observed anti-estrogenic effect of

smoking. Michnovicz and Fishman (1987) agree with the possibility of a role for estrogen antagonists as one of several multiple mechanisms.

Friedman, et al (1987) confirmed the absence of a smoking effect on estrogen level among post-menopausal women not under estrogen therapy, but did note a significant elevation of progesterone among smokers. They suggest that it is this increased progesterone level which partially protects smokers against endometrial cancer. Recent results from Khaw et al (1988) support this suggestion that the protective effect of smoking may be mediated by increased androgenic activity instead of reduced estrogenic activity.

ENDOMETRIAL CANCER

Each year, approximately 40,000 women in the United States are newly diagnosed with cancer of the endometrium, and about 3,000 women die from this disease (Tyler 1985). Known risk factors including obesity, certain medical conditions, reproductive factors, and socioeconomic status have been well-documented for over 10 years (Elwood 1977, Kelsey 1982), but evidence demonstrating an apparently protective effect of cigarette smoking has only recently been accumulating. It has been well-documented that smokers weigh less than non-smokers, that smoking cessation results in weight gain, and that this gain is relatively permanent for at least 25 years after cessation. (Blitzer 1977) Thus, smoking probably exerts it's protective effect both by weight control and by anti-estrogenic activity.

In a multi-center case-control study, Lesko, et al (1986) compared medical and reproductive histories, and data on drug, alcohol, and cigarette usage from 510 invasive endometrial cancer cases, ages 30

to 69, with data from 727 control women admitted for selected malignant conditions judged to be unrelated to cigarette use. Excluded from the control series were women who had a hysterectomy or bilateral oophorectomy. The median age of the cases was 59 years compared to 52 years for the controls. Twenty-two percent of the cases were current smokers; 29% of the controls currently smoked. In an analysis which controlled for age, body-mass, and duration of conjugated estrogen use, a rate ratio (RR) of 0.7 (0.5-1.0) for current smokers vs never-smokers was calculated. The RR for smokers of 25 cigarettes or more per day was 0.5 (0.3-0.8), while for those who smoked fewer cigarettes or were ex-smokers, the rate-ratios were not significantly different from unity. One finding of particular interest is that the effect of cigarette smoking on endometrial cancer risk depends on menopausal status. The rate ratio for heavy smokers among post-menopausal women was 0.5, while among pre-menopausal women the RR was 0.9. Exogenous estrogen use had no effect on the risk estimate. Although this study was well-designed and analyzed, the finding of an apparent protective effect of smoking has been dismissed as spurious by several critics. Alternative explanations for this finding include the

age difference between cases and controls (Nordenstam 1986), the possibility of a genetic predisposition both to smoking and to having a lower risk of endometrial cancer (Burch 1986), the use of some controls having colon-rectal cancer (Imrey 1986) or other cancers (Lashner 1986), and the possibility that intentional exclusions, such as of women with hysterectomies, or unintentional exclusions due to premature death from other causes among heavier smokers (Ravenholt 1986). For the most part, none of these criticisms appears to have much basis. Age differences were, in fact, controlled in the statistical analyses. The absence of reduced risk among former smokers argues against a genetic predisposition to both smoking and decreased disease risk. Lesko, et al (1986) noted that the colo-rectal controls had similar smoking histories as the other control patients, and that the neoplastic diseases included in the control series had not been previously associated with smoking. Furthermore, they stated that the proportion of current smokers among the controls was similar to that among women in the general population. Nevertheless, the use of control subjects without tobacco-related diseases probably would tend to decrease the rate ratio for smoking. The argument that smokers might die from a tobacco-related death

before they would enter into a study as a case is faulty because it would also preclude their entering as a control. In any event, the use of cancer patients as controls in the present study helps to ameliorate any potential problem. Premature death related to smoking would have to have occurred at different rates between women destined to have endometrial cancer and those destined to have other (control series) cancers.

Lawrence, et al (1987), using a population-based case-control design, selected from hospital files in upstate New York women ages 40 to 69 diagnosed as having early-stage endometrial cancer. These cases were confirmed histologically. Controls were selected from motor vehicle files, and were matched by county of residence and age to each case. Medical, reproductive, and smoking histories were collected by in-person interviews. Smokers of a pack or less per day had a relative risk of 0.7 compared to non-smokers, while those smoking more than one pack per day had a risk of 0.5. Among former smokers the corresponding relative risks were 1.0 and 0.60. Among both pre- and post-menopausal women, the relative risk for smokers compared to non-smokers was 0.6. Although these reduced

risks are not statistically significant, a real reduction in risk among pre-menopausal women could not be ruled out. There was no significant dose-response trend in risk reduction among ex-smokers. This study was the first to examine the combined effects of smoking and weight on the risk of endometrial cancer. This study found a modification by smoking of the effect of weight on increasing cancer risk. The largest reduction in risk for smoking occurred in the heaviest women, while no effect due to smoking was found in those weighing less than 140 pounds. Among non-smokers, the estimated disease risk increased up to five-fold with increasing body weight, while among smokers, the risk increased only 40%. Furthermore, among post-menopausal women who did not use exogenous estrogens, relative risk significantly increased with increasing weight, reaching 11.6 for those weighing over 180 pounds. The relative risk did not increase with increasing weight among smokers.

Smith, et al (1984) also used a population-based cancer registry to identify endometrial cancer cases and controls. Controls were frequency-matched by age to the cases, and excluded women with

cancer of the reproductive organs. The joint effect of smoking and weight on risk differed between pre- and post-menopausal women. In the pre-menopausal group, the risk to smokers compared to non-smokers was slightly increased among women with lower body size, but was increased less for heavier women. In neither instance was the risk statistically significantly raised. Among post-menopausal women, in contrast, smokers had lowered risk compared to non-smokers, with the effect being most evident among smaller women. Again, the risk reductions were not statistically significant.

In a recent case-control study of female reproductive cancers, Stockwell and Lyman (1987) compared 1,374 endometrial cancer cases identified through a state-wide cancer registry in Florida with 3,921 controls having diagnoses of either colon cancer, rectal cancer, cutaneous melanoma, or endocrine neoplasms (sites not having a recognized association with smoking). Compared to the cases, the control population was older and more likely to be divorced or widowed. Endometrial cancer risk was not significantly decreased for women who smoked less than a pack per day, but showed a significant inverse dose-response relationship for smokers of more

than a pack per day (0.7-0.5). Former smokers' risks were comparable, although the amount they smoked was not taken into account. The reduced risk was exclusive to women age 50 and older, and while the use of 50 as a surrogate for menopausal status might be questioned, the authors indicated a natural bimodal risk distribution centered at that point, and a median age of menopause in the U.S. at age 52. The use of cancer registry data also introduced some problems, notably the complete absence of data on weight, parity, and exogenous hormone use, as well as tobacco usage for some 25% of the subjects. Nevertheless, the findings compare well with other studies which had more or better information on these factors.

Baron, et al (1986) compared cigarette usage among 476 endometrial cancer cases ages 40-89, with that of 2,128 non-malignant disease control subjects admitted to the same hospital as the cases. Excluded from the control series were women diagnosed with respiratory or circulatory system diseases. Smokers with a history of 15 or more pack-years had an odds ratio, adjusted for other potentially confounding factors, of 0.6 (0.4-0.9) compared to non-smokers, and a

significant inverse dose-response relationship. It is unlikely that this finding was due to differential exogenous estrogen use between smokers and non-smokers since the data were collected between 1957 and 1965, before estrogen use increased in the late 1960's. Smoking rates among women ages 40-89 were lower than those among women born more recently, and the highest exposure category, 15 pack/years or more, represents a comparatively modest exposure. Furthermore, since current smoking status was not assessed, and other studies have shown lower risk for current rather than former smokers, this study would tend to underestimate the effect of recent smoking only.

Franks, et al (1987) used histologically confirmed cases of endometrial cancer between the ages of 20 and 55, and controls selected by random digit dialing in the same geographic areas as the cases. Analyses were based on information obtained from post-menopausal women over age 40 (106 cases, 528 controls). Cases were more likely than controls to be older, obese and to have never used oral contraceptives. The relative risk for endometrial cancer for women who continued to smoke after menopause was 0.5 (0.3-0.8) compared to non-smokers, in agreement with the findings of

Lawrence, et al (1987) The effect was similar among users and non-users of exogenous estrogens. Post-menopausal non-smokers who did not use estrogen replacement therapy had significantly excess risk, 3.8 (1.7-8.2), compared to smokers. Thus, the risk of endometrial cancer among post-menopausal women between 40 and 55 years of age is the same for users of both exogenous estrogens and cigarettes as it is for non-users of both. Though excluded from this study, post-menopausal women who quit smoking before menopause had reduced risk intermediate between, but not significantly different from the non-smokers and post-menopausal smokers. These results confirm the earlier findings of Weiss, et al (1980) of a reduction due to cigarette smoking in the increased risk from exogenous estrogen use. While the excess risk from estrogen therapy was not totally nullified by smoking in this earlier study, the reduction was greater for longer duration of estrogen use, amounting to an almost five-fold reduction among those women using estrogen for eight or more years.

The apparent protective effect of smoking on the risk of endometrial cancer received further confirmation in a recent study conducted in

Milan (Levi 1987). The study population comprised 357 women with histologically confirmed endometrial cancer, and controls admitted for acute conditions other than malignant, hormonal, gynecological, or smoking-related diseases, diseases associated with factors known to be related to endometrial cancer, or who had undergone hysterectomies comprised the study population. Cases were older, more frequently nulliparous, had greater body mass, were more educated, and had a later menopause. The age-adjusted relative risk for current smokers compared to non-smokers was 0.5 (0.3-0.7); for ex-smokers the risk was 0.8 (0.5-1.4). Dichotomization of amount smoked revealed no dose-response relationship. In contrast to other studies, neither body mass, menopausal status, nor exogenous estrogen use affected the risk estimates.

The study by Tyler, et al (1985) had equivocal results related to the effect of smoking on the risk of endometrial cancer among women under the age of 55. This population-based case-control study involved 437 cases and 3,200 controls selected by random-digit dialing in the same geographic area as the cases. Cases tended to be older, heavier, nulliparous, and to have consumed less alcohol. Relative

risks for current smokers showed a non-significant 20% deficit compared to non-smokers, and did not differ in pack/years smoked. The risk to former smokers was equivalent to that among non-smokers. When risk factors were considered jointly using logistic regression procedures, statistically significantly reduced risks were found for smokers who were post-menopausal or who had used estrogens. While the magnitude of the effect of smoking on lowering risk is not as evident as in other studies, these results do conform well with regard to the modification of risk due to estrogen use and menopausal status. They may also demonstrate, as pointed out by Baron, (1984) that the effect of cigarette smoking may be weaker in the younger age groups composing this study. It should be noted, however, that this study did not consider socioeconomic status, which had previously been found to be related to risk (Elwood 1977).

BREAST CANCER

Results from studies of breast cancer and smoking are less consistent in demonstrating a reduction of risk than those for endometrial cancer. Neither the study by Smith, et al (1984), which found no significant effect of smoking on endometrial cancer, nor the study by Stockwell and Lyman (1987), which found a protective effect, found any significant effect of smoking on breast cancer risk. In contrast, two of the largest prospective studies (Hammond 1966, Doll 1980) found generally lower breast cancer death rates among smokers than non-smokers. In the former study, among women aged 45-64 the ratio of the breast cancer mortality rate in smokers to that in "never-smokers" was 0.8; for heavier smokers that ratio was 0.8. Among women ages 65-79 the corresponding ratios were 1.0 and 1.1.

In the Doll, et al study of female British doctors, the annual breast cancer mortality rate for smokers of 25 cigarettes or more per day was 40 per 100,000 population; for smokers of 15-24 per day the rate

was 73 per 100,000; for smokers of 1-14 per day the rate was 50 per 100,000; and for ex-smokers the rate was 59 per 100,000. All of these rates were lower than the rate of 77 per 100,000 found among non-smokers.

Vessey, et al (1979, 1983) demonstrated a large protective effect of smoking on breast cancer incidence in a study of 1,176 breast cancer patients and age- and parity-matched controls. Cases were married women ages 16-50, whose cancer was newly diagnosed and histologically confirmed. Matching controls were selected from patients admitted for acute medical or surgical conditions or for routine elective surgery. Medical, obstetric, menstrual, contraceptive, and social histories were collected by personal interview. The relative risk for heavy smokers (15 cigarettes or more per day) vs non-smokers was 0.5, and showed a highly statistically significant inverse trend with amount smoked. Adjustment for factors which differed between cases and controls reduced the inverse association slightly (0.7). The authors attributed this unexpected finding to the unrepresentative nature of smoking habits among the hospitalized controls. That is, hospitalized controls would

more likely be smokers than would community controls, resulting in a lower ratio of smoking cases to controls and an apparent protective effect of smoking on the disease. This explanation, however, is not as tenable as for other studies using hospitalized controls since these women were admitted for acute conditions or surgical procedures which probably were not related to their smoking.

O'Connell, et al (1987) used community controls selected from the same catchment area as hospitalized cases in order to avoid this potential selection bias. However, compared to controls the 276 primary breast cancer cases were older, less obese, more educated, and more likely to be nulliparous, have a family history of breast cancer, and not use oral contraceptives. Odds ratios for current smoking, controlling for the potentially confounding effects of age, race, estrogen use, oral contraceptive use, and alcohol consumption were not statistically significantly reduced, but nonetheless showed a significant inverse trend with amount smoked. These risk estimates were 0.8 (0.5-1.1) for current smokers of a pack or less per day, 0.6 (0.3-1.1) for smokers of more than a pack per day, and 1.2 (0.8-1.7) for former smokers. The effect was similar in pre- and post-menopausal

women; 0.9 for pre-menopausal current smokers of 1-20 cigarettes per day, 0.4 for smokers of more than 20 cigarettes per day, and 1.2 for ex-smokers. The respective risks among post-menopausal women were 0.7, 0.6, and 1.1. The apparent negative association might have been due to confounding by body mass, since the cases and controls differed with respect to this variable. Smokers are less obese; obesity is related to late menopause; and both obesity and late menopause are risk factors for breast cancer. However, the analysis indicated that neither body mass index nor age at menopause diluted the apparently protective effect of smoking.

A case-control study of participants in a multi-center breast cancer screening program found a similar, non-significantly elevated risk among former smokers and also among current smokers (Brinton 1986). The self-selected subjects who were interviewed about smoking history comprised 1547 cases and 1930 controls. Of those eligible for the interview, non-respondents among the cases were 15% more frequent than among the controls, primarily because of the death of the study subject. If these deaths were more frequent among non-smoking cases than non-smoking controls, a possible result of a

protective effect of smoking, the estimates of relative risk might be biased toward apparently higher risk associated with smoking. The age-adjusted relative risks for current smokers compared to non-smokers was 1.17 (0.9-1.4), and for former smokers was 1.24 (1.0-1.5). For women who developed breast cancer after age 65, however, there was a non-significantly reduced risk of 0.6 (0.4-1.0). Risk estimates showed no real trend by duration of smoking or by amount smoked, and smokers showed no reduction in median age at menopause. Multivariate analysis controlling for the effect of other potential risk factors had no influence on the lack of an association with smoking. Of course, it is unlikely that analytic control for surrogate measures such as socioeconomic status totally controls for the potential confounding effect of risk factors such as dietary differences, with which they are correlated. The absence of an effect of smoking on lowering the age at menopause is puzzling, given that several studies had previously noted this effect. This may indicate some unknown bias operating in this study which may explain the absence of an inverse association with smoking.

Rosenberg, et al (1984) had similar findings in their study of women ages 30-69, hospitalized with breast cancer, and controls admitted for other malignancies. The control series excluded women with diagnoses of lung cancer, endometrial cancer, or any other cancer associated with smoking or age at menopause. Control patients' diagnoses comprised cancers of the ovary, colon or rectum, or malignant melanoma. Median age of the two study groups was equivalent. The estimated relative risks for current smokers among the 717 cases compared to the 2,160 controls were 1.3 (0.9-1.8) for light smokers (1-14 per day), 1.0 ((0.8-1.4) for smokers of 15-24 cigarettes per day, 1.1 (0.8-1.6) for smokers of 25 or more cigarettes per day, and 1.1 (0.8-1.3) for ex-smokers. A very modest protective effect of smoking could not be ruled out in this study despite its large sample size, although the evidence is against a reduction of 20 percent or more in current smokers. As with the previous study, personal interviews could not be blinded, and the possibility of response or interviewer bias cannot be excluded.

A cohort study by Hiatt and Fireman (1986) similarly failed to demonstrate a protective effect of smoking on breast cancer, despite

the finding that the mean age at menopause was earlier for current smokers. 84,172 women ages 20-84, who were members of a Northern California pre-paid health plan, and who had provided information on smoking habits, were enrolled in this prospective study. Breast cancer cases occurring from 1971-1980 among these women were identified from hospital discharge files and the California Tumor Registry. The mean length of follow-up from the date of entry into the study was 10.5 years. Age-standardized breast cancer incidence rates were 1.27 per 1,000 person-years for non-smokers, 1.38 for current smokers, and 1.63 for ex-smokers. Relative risks were 1.0 (0.8-1.1) for light smokers compared to non-smokers, 1.2 (1.0-1.4) for moderate smokers, 1.2 (0.9-1.6) for heavy smokers, and 1.2 (1.0-1.4) for ex-smokers. The higher risk for moderate compared to heavy smokers, and for ex-smokers compared to both non-smokers and current smokers is curious, and may indicate some related lifestyle factor that occurred differentially between cases and controls, possibly accounting for the lack of a protective effect of smoking. The known risk factor of obesity also was found not to affect risk. The power of this study was sufficient, with 95% confidence to rule out a protective effect of smoking of 5% or more. As to why age at

menopause was inversely associated with smoking and with breast cancer risk, while the risk was still somewhat elevated among smokers, the authors suggest that smoking exerts both a direct, harmful effect on breast tissue and an indirect, protective effect through reduction of estrogen levels.

Schecter, et al (1985) conducted a case-control study among women ages 40-59 who participated in a multicenter breast cancer screening program in Canada. Smoking was found to increase risk twofold among pre-menopausal women who ever smoked, but among post-menopausal women, no overall association was detected. No information on dietary habits was collected, so possible undetected confounding by this factor may explain the finding of excess risk. Similarly, the choice to participate in the screening program may be associated with unknown risk or lifestyle factors which determine or are associated with the development of breast cancer.

Several studies of other breast cancer risk factors also have examined the effect of smoking. Paffenbarger, et al (1979) found that a smaller percentage (52.3%) of cases than medical (55.4%) or surgical (55.7%)

controls reported having ever smoked. This, of course, may not reflect the effect of current smoking on risk. No information was given regarding the diagnoses included in the control groups, nor were the effects of other risk factors taken into account when examining the smoking effect.

Studies of alcohol consumption and breast cancer have indicated correlations between smoking and alcohol use, but have not been consistent in determining the risks of the latter. Recently, Schatzkin, et al (1987) found moderate alcohol consumption to elevate breast cancer risk by 50-100% in a large cohort study based on a sample of the U.S. population. The percentage of women who reported drinking increased with increasing number of pack/years smoked.

In a prospective study of nurses published at the same time, Willett, et al (1987) found a similar risk for moderate alcohol intake, and observed that the association tended to be weaker among women who had never smoked cigarettes. Smoking, itself, was not significantly related to risk. One possible flaw in this study was its failure to determine family occurrence of breast cancer after the subject first

entered into the study, although the subjects were followed for up to nine years.

Harvey, et al (1987) investigated alcohol consumption among 1,799 breast cancer cases and 2,208 controls who participated in the Breast Cancer Detection Demonstration Project. They found a statistically significant trend of increasing risk with increasing average weekly alcohol intake, and an increased risk associated with two or more drinks per day. Although the study suffered from lack of information on dietary habits, the association between moderate alcohol consumption, particularly before age 30, and subsequent elevated breast cancer risk is coherent with other epidemiologic evidence.

A French case-control study (Le Monique 1984) of the effect of alcohol consumption found a relative risk of 1.5 for drinking, similar to a previous U.S. case-control study (Rosenberg 1982), and a small non-significant excess risk associated with current smoking. However, only seven percent of all subjects were current smokers. The observed excess risk from alcohol in these studies might mask the protective effect of smoking seen in some of the studies reviewed

above, since the two factors are highly correlated and have opposite effects on risk.

Another facet of the smoking/breast cancer association was demonstrated in a Japanese study which investigated risk factors associated with multiple primary cancers in breast cancer patients (Kato 1986). Comparisons were made between patients with multiple primary cancers occurring after or concurrently with breast cancer and patients with unilateral breast cancer. A multiple logistic regression analysis indicated that smoking more than 10 cigarettes per day significantly decreased the risk of multiple primary cancers (RR=0.23). Risk factors for breast cancer in general also tended to increase the risk of second primaries. Since medical records were used to obtain smoking histories, and it is not clear how accurate these records are in Japan, these results are open to some doubt.

None of these studies considered differences between estrogen receptor (ER)-rich and (ER)-poor breast cancers and differences in the risk factors for each. If the mechanism by which risk factors for the disease operate is associated with alteration of the ER status of

the cells from which the cancer develops, and if the ER status of the fully-developed tumor reflects the receptor status of the original cells, ER-rich and ER-poor tumors would differ with respect to those risk factors. Differences in ER status between populations being compared could, therefore, account for some of the differences in the results from the studies discussed above. McTiernan, et al (1986) calculated relative risks for ER-rich and ER-poor breast cancers with respect to known breast cancer risk factors. They found several factors which were risk factors for one type but not the other. Cigarette smoking was not found to be a statistically significant risk factor for either type, although it reduced the risk of ER-poor tumors by 25% among current smokers and 16% among ex-smokers, compared to non-smokers. Essentially no difference was found for ER-rich tumors.

CONCLUSIONS

As previously discussed, consistency of results upon replication is strongly indicative of a causal relationship, particularly with differing study designs and populations. Similarly, consistency of results indicating a reduced risk among an exposed population strongly supports a protective effect due to that exposure. In the case of endometrial cancer and smoking, the consistent inverse dose-response relationship is evident and the close concordance of risk estimates among studies is remarkable. Clearly, the risk of endometrial cancer among smokers is half as great as that among non-smokers. This relationship appears to be affected by body weight and by exogenous estrogen use, as well as by menopausal status. The protective effect of smoking exerts itself more strongly among post-menopausal women and those who weigh less. It appears to cancel the increased risk due to usage of exogenous estrogens, particularly among long-time users.

While estimates of the actual incidence of endometrial cancer are imprecise due to misclassification, there does appear to be an

epidemic of the disease during recent years. The increasing incidence probably is due to increasing use of estrogen replacement therapy, although it may in part reflect better case-finding and changing diagnostic criteria. Smoking is likely to be a powerful moderating factor of this rise.

The inconsistency of results from epidemiologic studies of breast cancer risk due to cigarette smoking is undoubtedly due to the complex etiology of the disease. Additional research aimed at unraveling the specific hormonal components and mechanisms affecting the occurrence of the disease is needed. A role for smoking in lowering the risk of the disease is highly plausible, despite the varied results of the studies reviewed herein, because of strength of the findings in endometrial cancer studies of a relation to estrogen levels and to the additional avenue of weight reduction as a protective factor. The breast cancer/smoking results, by their inconsistency, exemplify the potential misinterpretation of epidemiologic studies that do not consider molecular, cellular, metabolic, or other unascertained differences among comparison subjects, such as

alcohol consumption, and differences in the effect of cigarette smoking on estrogen receptor-rich and ER-poor tumors.

Finally, it is worth conjecturing that in males the risk of other hormonally-dependent diseases, such as prostate cancer, might be reduced by smoking. Certainly, this subject should have been studied, but reports are absent from the literature.

COLON DISEASES

COLON CANCER

There is suggestive evidence in the literature of a protective effect of cigarette smoking on the risk of colon cancer. Over twenty years ago, Hammond (1966) found that the colon cancer mortality rate among women smokers ages 45-64 was 78% that of women who had never smoked cigarettes regularly. "Heavier" smokers had only about two-thirds the mortality rate of never-smokers. Among males in the study, no significant effect of smoking was noted. Data from the Framingham study support an inverse relationship between smoking and colon cancer incidence (Williams 1981). Fifty-eight colon cancer cases occurred among the 5,209 participants; 28 among males and 30 among females. A logistic regression analysis revealed a statistically significant inverse association between smoking level and colon cancer in both sexes. Smokers of a pack or more per day almost one quarter the rate of colon cancer as did non-smokers.

The population-based Third National Cancer Survey found that the relative odds of colon cancer for smokers compared to non-smokers were about 25% lower for males and 10% lower for females (Williams

1977). Among Japanese in Hawaii, the relative risk of colon cancer was found to be reduced by a third for male smokers of a pack or more per day compared with smokers of less than that amount and slightly reduced for tobacco users compared to non-users.

Only one study has focused specifically on the relationship between cigarette smoking and colorectal cancer (Sandler 1988). This study was a prospective follow-up of disease incidence over a 12-year period among over 25,000 women in Washington County, Maryland. Incident colorectal cancers were obtained from a county-wide registry and matching of residents' death certificates against the initial study population census provided the remainder of the cases. The census also provided information on smoking habits and demographic characteristics. The relative risk of developing colorectal cancer for ever smokers compared with non-smokers was significantly reduced (RR = 0.3, 0.2-0.4).

Age-adjustment eliminated the statistical significance of the reduced risk, however, after adjustment for differences in other factors, the relative risk for women smokers over age 50 again was reduced

(RR=0.6, 0.4-1.0). Age-specific relative risk suggest that the apparent protective effect of smoking on colorectal cancer risk in women is stronger at old ages. This may reflect partial mediation by the antiestrogenic effect of which showed that the incidence of colon cancer in women with children was 30%-50% less than in nulliparous women.

Few other studies have evaluated the effect due to smoking, and it is possible that lifestyle factors which increase the risk of colon cancer and which are independently associated with smoking, may mask its possible protective effect. Apparently, alcohol is one of these factors. Wu, et al (1987) in a prospective study of almost 12,000 residents of a retirement community found a twofold increase in colorectal cancer risk for daily alcohol drinkers. This excess reached statistical significance in males, but not in females. The study also indicated another possible factor which might mask a protective effect of cigarette smoking; i.e., body mass. This factor, as measured by Quetelet's index, was associated with elevated risk of colorectal cancer and is known to be inversely related to cigarette usage, as discussed previously.

ULCERATIVE COLITIS

Ulcerative colitis is a recurrent inflammatory and ulcerative disease of the colon and rectum, characterized clinically by rectal bleeding, diarrhea, abdominal pain, anorexia and weight loss (Kirsner 1982). Patients with total ulcerative colitis lasting longer than seven years are at increased risk for carcinoma of the colon and rectum, which develop earlier, and with a tendency toward multiple lesions.

A large body of evidence from epidemiologic studies conducted during the past decade demonstrates that the risk of ulcerative colitis is reduced among persons who smoke cigarettes. For example, the disease occurs more frequently among Mormons, who generally refrain from smoking (Penney 1983). More importantly, the remarkable concordance in the magnitude of the reduced risks observed in numerous studies, despite their different designs and study populations, lends plausibility to this hypothesized association, although the specific biological mechanisms for this phenomenon have not yet been confirmed.

Other scientific evidence, though possibly limited generalizability, dramatizes the inverse association. De Castella (1982) reported on a female who smoked a half-pack or less per day for fifteen years. Upon stopping at age 33, she developed ulcerative colitis, but when she started smoking again some nine months later, her symptoms disappeared within four weeks. Within five weeks after restarting eighteen months later, the symptoms reappeared. After five months she resumed smoking and they disappeared. A third time she stopped, and the symptoms reappeared, only to disappear again when she resumed smoking three months later. She attempted to stop twice more, with the recurrence of symptoms. She now smokes, as condoned by her medical advisors, and "remains well."

Roberts, et al (1982) reported on a woman who developed colitis in 1961. When she started smoking in 1964, the symptoms of the disease disappeared. Seven years later she stopped smoking and thereafter, relapsed. Her symptoms disappeared when she began smoking again. She repeated this several times with the same results. Currently, 16mg per day of nicotine (gum) maintains her remission.

As interesting and suggestive as these anecdotal reports are, epidemiologic studies provide the incontrovertible evidence of an inverse association between smoking and colitis. Harries, et al (1982) conducted a case-control study, using questionnaires mailed to colitis and Crohn's disease patients (cases), and to controls who had attended a fracture clinic and who were matched for age and sex, but not socioeconomic status, to the cases. The study population comprised 230 ulcerative colitis patients, 190 Crohn's disease patients, and 230 controls. 8% of the colitis patients, 42% of the Crohn's disease patients, and 44% of the controls were current smokers. The difference in the proportion of smokers among the colitis patients compared with the other groups was highly statistically significant. 48% of the colitis patients had never smoked, compared to 30% of the Crohn's disease patients and 36% of the controls. These differences also were statistically significant. 40% of the colitis patients were ex-smokers, averaging 13 years since stopping. Only 27% of the Crohn's disease patients and 20% of the controls had quit. Part of this apparently increased risk to ex-smokers might have been due to significantly more (76%) of the

patients with colitis coming from non-smoking households compared to the Crohn's disease patients (60%) and the controls (51%). Among colitis patients, 82% of non-smokers came from non-smoking households, whereas 78% of the smokers came from smoking households.

Jick and Walker (1983) selected ulcerative colitis patients and controls from data collected previously in a multinational study of some 45,000 patients, and in a study of some 25,000 patients admitted to Boston area hospitals. Data from a total of 239 colitis patients and 956 controls were reviewed for information on patients' smoking histories. Overall, the risk of ulcerative colitis in current smokers was 0.31 (0.22-0.43) compared to non-smokers. The lower risk was present in every age group, with more reduction in men than in women and more in heavier than in lighter smokers. In both sexes, there was little additional reduction in risk associated with smoking more than 1 pack per day. For ex-smokers, the risk was 1.16, though not statistically significant. The lowered risk among current smokers was present in both studies, and in each country in the multinational effort. The rather low relative risk for current

smokers might, in part, be due to the exclusion from the control group of persons with diagnoses of cancer, cardiovascular disease, or respiratory illnesses.

A small Czechoslovakia study found somewhat higher risk estimates, although the methodology and statistical analyses were not reported in detail (Bures 1982). Odds ratios for male colitis patients compared to male Crohn's disease patients were 0.4 for current smoking and 1.0 for non-smoking. In females, the respective were odds ratios 0.5 and 1.2. The authors also examined data from 22,060 autopsies conducted over 20 years, and discovered twice as many smokers as non-smokers among Crohn's disease subjects, and half as many in ulcerative colitis subjects. Another small study showed somewhat higher proportions of smokers in each group, but had an equivalent relative risk; i.e. 10 of 40 colitis patients smoked compared to 22 of 35 Crohn's patients (Entrican 1986). These findings, though similar to those from other studies, must be viewed with caution because of the limited information contained in the reports.

Holdstock, et al (1984) interviewed 102 outpatients diagnosed with ulcerative colitis, 96 with Crohn's colitis, and 54 with Crohn's disease of the small bowel. Only 8% of the colitis patients smoked, compared with 25% of the Crohn's colitis patients and 52% of the small bowel Crohn's disease patients. The respective proportions of ex-smokers were 32%, 30% and 13%. However, the large differences between colitis and Crohn's disease patients are somewhat misleading with regard to risk, since most studies indicate increased risk of Crohn's disease in smokers. A better comparison group would be persons not having inflammatory bowel diseases, although a particular design, such as used in a recent study might not allow this (Cope 1986). Here, colonoscopy patients were interviewed, then divided into an ulcerative colitis group and a control group (the latter containing persons diagnosed with diverticular disease, irritable bowel syndrome, colonic carcinoma, or colonic polyps). 13% of the case group were smokers while 42% of the controls currently smoked.

The magnitude of the reduced risk among smokers was slightly less in a recent study from Milan which avoided a comparison between

colitis and Crohn's disease patients (Franceschi 1987). In this hospital-based investigation, cases included both ulcerative colitis and Crohn's disease patients, while controls were hospitalized for acute conditions, and those with tobacco-related, malignant, respiratory, or digestive diseases were excluded. The estimated relative risk of colitis in current smokers was 0.6 (0.3-1.0) with a significant trend of lower risk associated with greater amount smoked, and of lower risk with longer duration of smoking. Among ex-smokers, the relative risk was 2.6 (1.4-4.6). In contrast, among patients with Crohn's disease, both current and ex-smokers had relative risks significantly greater than unity (3.2 and 3.9). While 26 of 46 ex-smokers with colitis quit after the first appearance of symptoms, only 4.3% cited "abdominal disturbances" as the reason. Heavier smokers quit more frequently than did light smokers, but quitting was not associated with appearance of symptoms. Because the control group in this study excluded patients with diseases thought to be related to tobacco use, a necessary methodological consideration in any hospital-based investigation, its risk estimates are probably more precise than the studies previously reviewed here. However, population-based studies are preferable, so that a trade-off

between artificially under-representing or over-representing smokers among controls does not have to be made.

Logan, et al (1984) and Somerville, et al (1984) used case-control designs for studying smoking among patients with ulcerative colitis or Crohn's disease. In the former, questionnaires were mailed to 124 patients and for each case to two controls who were selected from the records of each case's physician, and matched by age and sex to the case. The relative risk for non-smokers compared to current smokers was 3.8 (2.0-6.9); the association remained when smoking status prior to three months before the onset of clinical disease was used. In the latter, a case-control study of Crohn's disease, relative risks of 4.0 (1.9-8.1) for ever-smoked, 3.5 (1.8-6.6) for current smokers, and 4.8 (2.4-9.7) for smokers at time of disease onset were found.

Similarly, Tobin, et al (1987) sent questionnaires to 280 patients (143 ulcerative colitis, 137 Crohn's disease) and an equal number of age- and sex-matched community controls. Great care apparently was taken to avoid information bias, particularly in framing the questions regarding smoking habits. The relative risk for colitis among

current smokers at the time of the interview was lower than any previous study, 0.2 (0.1-0.3). The relative risk was equivalent for smoking status at the onset of symptoms. The risk for ex-smokers was greater than for non-smokers, 1.5 (0.8-2.8), but was not statistically significantly higher. In contrast, among Crohn's disease patients, the risk for current smokers was 1.9 and for ex-smokers was 1.6, though neither was significant. There was a significant trend of decreasing relative risk associated with increasing amount smoked per day. 76% of ex-smokers with colitis stopped before onset. Results for a case-control study by Benoni and Nilsson (1987) which compared patients having inflammatory bowel disease with community controls found reduced risk of ulcerative colitis and elevated risk of Crohn's disease for current smokers which were of the same magnitude as those of Tobin, et al. A more recent Swedish study (Lindberg 1988), which used a similar study population, found a statistically significantly reduced colitis relative risk of 0.7 for smokers compared with never smokers. In this study, ex-smokers had a significantly elevated relative risk. The risk of Crohn's disease was elevated for current and former smokers, although only the former reached statistical significance. It is

possible in these two studies that differential selection of cases and controls (i.e. cases from a hospital population, controls from the community) might have resulted in over-representation of smokers among cases. Nonetheless, the results of Tobin, et al (1987) confirm others' observations that associations with smoking antedate the onset of inflammatory disease (Franceschi 1987), and that they are, therefore, more likely to be protective.

Boyco, et al (1987) seem to have overcome some of the aforementioned problems of previous hospital-based studies by selecting both cases and controls from enrollees in a Health Maintenance Program, and by eliminating subjects with Crohn's disease. 250 subjects with colitis or proctitis, and an equal number of age- and sex-matched controls were selected from an overall population of 304,000. Telephone interviews were conducted to obtain smoking histories. The estimated relative risk of ulcerative colitis was 0.6 (0.4-1.0) for current smokers (at the time of onset of symptoms) vs never-smokers; and 2.0 (1.1-3.7) for ex-smokers vs never-smokers. The magnitude of these risks was unchanged by adjustment for coffee or alcohol consumption. Among current smokers, relative risks for 1-20

pack/years were not significantly different from unity, but the RR for 21 or more pack/years was 0.5 (1.3-17.6). Among ex-smokers the excess risk was also significant in this duration category. In addition, the authors reanalyzed data from two previous outpatient studies (Harries 1982 and Logan 1984) and one inpatient study (Jick 1983) to assess the risks to ex-smokers. They found agreement in the estimated relative risks with their own estimates, although the risks in the Jick study were slightly lower, perhaps due to over-representation of former smokers among controls. (This may be similar to the recognized over-representation of present smokers in hospital populations). It has been suggested that differential response rates between cases and controls (85% vs 62%) might explain the Boyco, et al (1987) findings if smokers were over-represented among the non-responders (Logan 1987). It has been found that non-respondents are more likely to be smokers (Criqui 1978). More recently in a similar study Sandler and Holland (1988) sent questionnaires to inflammatory bowel disease cases drawn from the rosters of three chapters of the National Foundation for Ileitis and Colitis and to neighborhood controls. Their findings with regard to ulcerative colitis also were similar; i.e. a significantly decreased

odds ration (0.5, 95% CI=0.3-0.9) with the lowest risk found for the heaviest smokers.

Of course, dietary habits could conceivably confound or partially explain these results. Thus, Thornton, et al (1980) compared dietary histories of 30 colitis patients and fracture clinic controls. They failed to find any significant differences, (in contrast to their previous study of Crohn's disease patients), indicating that Crohn's disease and ulcerative colitis "despite their similarities, ...do not have identical etiologies." A later study of 30 patients with colitis, 30 with Crohn's, and two groups of matched controls from a fracture clinic demonstrated no difference between smokers and non-smokers with regard to dietary habits, although compared to controls the Crohn's patients consumed more refined sugar whereas no difference was noted for the colitis patients (Thornton 1985). Katschinski, et al (1988) confirmed the positive association with refined sugar intake, although excess risk was evident only in ex-smokers and never-smokers.